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PATENT COOPERATION TREATY

CONFIRMATION

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *day/month/year*	09 NOV 2004
Applicant's or agent's file reference 10104SG53/KJR/PDR	IMPORTANT NOTIFICATION

International Application No.	International Filing Date	Priority Date
PCT/SG2003/000169	11 July 2003	12 July 2002

Applicant
NATIONAL UNIVERSTIY OF SINGAPORE et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translations to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide

Name and mailing address of the IPEA/AU	Authorized officer
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	LEXIE PRESS Telephone No. (02) 6283 2677

PATENT COOPERATION TREATY

CONFIRMATION

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 10104SG53/KJR/PDR	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. **PCT/SG2003/000169**	International Filing Date *(day/month/year)* 11 July 2003	Priority Date *(day/month/year)* 12 July 2002
International Patent Classification (IPC) or national classification and IPC **Int. Cl.**[7] C12N 5/02		
Applicant NATIONAL UNIVERSTIY OF SINGAPORE et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheet(s).

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand 6 February 2004	Date of completion of the report 4 November 2004
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **LEXIE PRESS** Telephone No. (02) 6283 2677

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SG2003/000169

I. Basis of the report

1. With regard to the elements of the international application:*

- [X] the international application as originally filed.
- [ ] the description, pages , as originally filed,
  pages , filed with the demand,
  pages , received on with the letter of
- [ ] the claims, pages , as originally filed,
  pages , as amended (together with any statement) under Article 19,
  pages , filed with the demand,
  pages , received on with the letter of
- [ ] the drawings, pages , as originally filed,
  pages , filed with the demand,
  pages , received on with the letter of
- [ ] the sequence listing part of the description:
  pages , as originally filed
  pages , filed with the demand
  pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

- [ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- [ ] the language of publication of the international application (under Rule 48.3(b)).
- [ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- [ ] contained in the international application in written form.
- [ ] filed together with the international application in computer readable form.
- [ ] furnished subsequently to this Authority in written form.
- [ ] furnished subsequently to this Authority in computer readable form.
- [ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- [ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. [ ] The amendments have resulted in the cancellation of:
   - [ ] the description, pages
   - [ ] the claims, Nos.
   - [ ] the drawings, sheets/fig.

5. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-14	YES
	Claims -	NO
Inventive step (IS)	Claims 1-14	YES
	Claims -	NO
Industrial applicability (IA)	Claims 1-14	YES
	Claims -	NO

2. Citations and explanations (Rule 70.7)

The invention relates to a hemangioblast cell line capable of *in vitro* differentiation into hematopoietic and endothelial cells. The cells are not immunoreactive with CD34, Pecam-1, Flk-1, Tie-2, Sca-1, Thy-1 and P-selectin markers. An illustrative example of the cell line derived from mouse is deposited under ATCC PTA-4300.

The Applicant's response of 26 October 2004 has been considered, and it does not impact on the statement related to novelty and inventiveness issued in the previous Written Opinions. Documents 1 to 5 identified in the International Search Report have been considered for the basis of this Examination Report.

D1 Kocher et al (2001) Nature Medicine Vol 7(4): 430-436

D2 Schuh et al (1999) Proc. Natl. Acad. Sci. Vol 96: 2159-2164

D3 Minehata et al (2001) Blood. Vol 99 (7): 2360-2368

D4 WO 2000/11139 A1

D5 EP 1229116 A1

D1 discloses a 98% pure preparation of $CD34^+$ cells, derived from human adult bone marrow, with phenotypic and functional characteristics of hemangioblasts. The cells can be used to induce vasculogenesis and angiogenesis *in vivo*. The hemangioblast cells of the present invention are $CD34^-$ and consequently, the citation does not impact on the novelty or inventiveness of any of the claims.

D2 discloses a colony of Flk^- blast cells derived from embryonic stem cells capable of differentiation into hematopoietic and endothelial cells *in vitro*. D2 does not explicitly teach a purified preparation of hemangioblast cells that are $CD34^-$ and does not impact on the novelty or inventiveness of any of the claims.

D3 and D5 are analogous and disclose a method for preparing a cell population containing hemangioblasts from AGM primary cell cultures, based on positive selection of cells expressing PCLP1. PCLP+/CD45- cells have the potential to differentiate into hematopoietic and endothelial cells. There is no evidence that the selected hemangioblast cell fractions have the same $CD34^-/Flk^-$ phenotype characteristic of the cells of the present invention. Therefore, the present claims are novel and inventive over both D3 and D5.

(continued in supplemental box)

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The Applicant's response of the 26 October 2004 has been considered with regard to descriptive support for claims 1 to 3. This IPEA maintains the opinion that the claims are not fully supported by the description and claim subject matter in terms of a desired result, rather than by the technical features necessary for achieving the result.

Hemangioblasts and methods of their production are known in the art (see D1-D5) and the advance over the prior art resides in one particular method of establishing hemangioblasts of the phenotype as defined in claims 1 and 2. The Attorney asserts that the specification discloses more than one method of establishing hemangioblasts of the desired phenotype. However, it is not agreed that this is the case, the specification discloses three different cell sources (embryo, embryonic stem cell, and bone marrow) that are utilised in the method, rather than different methods. Regardless of the cell source, the one particular method disclosed in the application comprises culturing the cell source on a feeder layer, selection of colonies of adherent fibroblastic cells with loosely attached rapidly dividing round cells having ring-like cells at their edges, and testing the cells in the selected colonies for ability to differentiate into both endothelial and hematopoietic cells.

The Attorney also asserts that because the hemangioblasts of claims 1 and 2 are novel and the Applicant is the first to establish hemangioblasts from an embryo, they are entitled to a corresponding breadth of claiming. While it is acknowledged that the claimed hemangioblasts are novel, they are also products of the specific method. This one method is not a blueprint for all means of producing hemangioblasts of the desired characteristics and phenotype. Consequently, the description only supports hemangioblasts when prepared by the disclosed method.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of V

D4 describes a preparation of hemangioblasts isolated from cord blood, methods of expanding the hemangioblast population and their use in generating endothelial cells and hematopoietic cells. The citation does not disclose hemangioblasts with a $CD34^-/Flk^-$ phenotype and does not impact on the novelty or inventiveness of any of the claims.

In summary, none of the cited documents disclose or suggest a purified hemangioblast preparation of cells that are not immunoreactive with CD34, Pecam-1, Flk-1, Tie-2, Sca-1, Thy-1 and P-selectin markers or the specific cell line deposited under ATCC PTA-4300. Therefore, the subject matter of the searched claims meet the criteria set forth in PCT Articles 33(2) and 33(3) for novelty and inventive step.